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MEMORANDUM

5 July, 2005

TO: Jenny Craig, EPA/OPAR

CC: Nona Smoke, EPA/OPAR

FROM: Tyra Gettleman and Henry Roman, IEc

SUBJECT: Benzene Health Effects Literature Review

INTRODUCTION

In June 2003, Industrial Economics, Incorporated (IEc) and EPA presented to the Health Effects Subcommittee (HES) of the Scientific Advisory Board Council (SAB) an analytical plan for a case study estimating the health benefits of benzene reductions in the Houston area under the Clean Air Act Amendments (CAAA) of 1990. The analytical plan proposed to quantitatively estimate avoided cases of leukemia (all types) using a life-table approach that would allow us to assess the effects of changes in benzene exposures over time, and to implement a lag for the realization of benefits. The proposed life table approach would use risk estimates for leukemia from an analysis of an occupational cohort by Crump (1994), and would assume a five-year lag. The plan also proposed to semi-quantitatively assess changes in risk of decreased white blood cell counts by estimating changes in the numbers of individuals exposed above EPA's reference concentration (RfC) for benzene, and to qualitatively discuss other health endpoints (e.g., non-Hodgkin's lymphoma) that have been associated with benzene exposure in the literature.

The SAB HES in its response letter (EPA, 2004) made several recommendations concerning the analytical plan. They suggested that EPA take a closer look at studies of a large Chinese worker cohort exposed to benzene as a possible replacement for the risk estimates of Crump, which are based on a smaller cohort with fewer cases of leukemia. They also recommended that EPA consider studies of this larger cohort that suggest a non-linear

concentration-response function for leukemia. Finally, they suggested that the proposed lag of five years did not make full use of available information, and recommended that EPA consider revising its approach to the lag issue after reviewing available epidemiological data.

IEc has conducted a literature review of the health effects of benzene to explore whether the analytical plan should be revised, either in response to the studies cited by the SAB, or because recent literature suggests additional health endpoints for us to consider in the Houston case study. The literature search thus focused on identifying evidence of non-leukemia health effects, defining the leukemia/benzene dose-response function, and characterizing the lag between benzene exposure and onset of leukemia. This review is not intended to replace EPA's evaluation of the literature on benzene health effects that was developed to support the benzene Integrated Risk Information System (IRIS) profile, but rather to complement that review with more recent data that may assist EPA in refining its analytical plan for the benzene case study.

LITERATURE SEARCH APPROACH

We conducted a search of peer-reviewed literature published in the past ten years pertinent to the health benefits portion of the benzene case study analytical plan. We identified relevant studies using the Dialog search engine. We began with a broad search of studies of the health effects of benzene, including leukemia, and then added keyword terms in two subsequent searches to focus on the dose-response relationship between benzene and leukemia and the latency period for developing leukemia. In addition, we conducted more focused searches, using key words for specific health effects to ensure completeness.[1] We reviewed abstracts for those studies that we felt might be relevant to the literature review, based on the title. We then included all studies that we felt would provide valuable information on one of the three subject areas of the literature review, which included 46 studies.

RESULTS OF THE LITERATURE REVIEW

In this section, we present the results of our literature search grouped into three topic areas: evidence for specific health effects associated with benzene exposures; issues concerning the dose-response function for benzene-induced leukemia; and evidence of a lag period for the full realization of benefits following reductions in benzene exposure ("cessation lag"). In the first two sections, we both briefly review the conclusions that EPA reached in quantifying risk estimates for inhaled exposures of benzene in support of the IRIS profile, and we discuss the findings of additional studies uncovered during our literature search. In the third section, we discuss how latency estimates and other data from existing epidemiological studies help define the concept of cessation lag.

The literature review that we conducted focused on human studies. We reviewed 46 studies, including 21 cohort analyses, 12 case-control analyses, 8 reviews, 3 meta-analyses, 1

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[1] We used the following key words: "benzene" and "leukemia" and ("latency" or "lag time" or "incubation period") and "dose response" in various combinations. The more specific searches included "benzene" and the following key words: ("hematologic" or "blood"); "Chinese worker"; "non-Hodgkin's lymphoma"; "Hodgkin's" "disease or lymphoma"; "myelodysplastic syndrome"; "multiple myeloma"; and "lymphohematopoeitic."

cross-sectional study, and one exposure validation study. Exhibit 1 below displays studies we identified in our search, grouped by study type.

EXHIBIT 1 LITERATURE SEARCH RESULTS		
Cancer		
Study Type	*Citation*	*Endpoint(s)*
Case-Control	Finkelstein (2000)	Leukemia
Case-Control	Glass et al. (2003)	Leukemia, ANLL, CLL, CML, NHL, MM
Case-Control	Guenel et al. (2002)	Leukemia
Case-Control	Rushton and Romaniuk (1997)	Leukemia, AMML, CLL, ALL, CML
Case-Control	Schnatter et al. (1996a)	Leukemia, MM
Cohort	Adegoke et al. (2003)	Leukemia, ALL, AML, CML
Cohort	Bloemen et al. (2004)	Leukemia, CLL, ANLL, MM, NHL, HL
Cohort	Collins et al. (2003)	Leukemia, ANLL, CML, MM, NHL, HL
Cohort	Costantini et al. (2003)	Leukemia
Cohort	Crump (1994 & 1996)	Leukemia, AMML
Cohort	Hayes et al. (1997 & 2000)	Leukemia, ANLL, AML, CML, ALL, NHL
Cohort	Ireland et al. (1997)	Leukemia, MM, ANLL
Cohort	Paxton et al. (1987)	Leukemia
Cohort	Rinsky et al. (1981, 1987 & 2002)	Leukemia, MM, NHL
Cohort	Schnatter et al. (1996b)	Leukemia, AMML
Cohort	Silver et al. (2002)	Leukemia
Cohort	Sorahan et al. (2005)	Leukemia, AML, CML, CLL, NHL, HL
Cohort	Swaen et al. (2005)	Leukemia, MM, HL
Cohort	Wong (1995)	AMML, MM
Cohort	Yin et al. (1987 & 1996)	Leukemia, AML, CML, ALL, MM, NHL
Cohort/Case-Control	Rothman et al. (1997)	ANLL/MDS, Enzymatic genotypes
Exposure Validation	Dosemeci et al. (1996)	Validates exposure estimates in Chinese Worker Cohort
Meta-Analysis	Lamm et al. (2005)	NHL
Meta-Analysis	Sonoda et al. (2001)	MM
Meta-Analysis	Wong and Raabe (2000)	NHL
Review	Bergsagel et al. (1999)	MM
Review	Bezabeh et al. (1996)	MM
Review	Budinsky et al. (1999)	Exposure estimates in Chinese Worker Cohort
Review	Hayes et al. (2001)	Exposure estimates in Chinese Worker Cohort
Review	Savitz and Andrews (1997)	Leukemia and subtypes
Review	Utterback and Rinsky (1995)	Exposure estimates in Pliofilm Cohort
Review	Wong (1999 & 2002)	Exposure estimates in Chinese Worker Cohort
Non-Cancer		
Case-Control	Lan et al. (2004)	Decreased lymphocytes
Case-Control	Qu et al. (2002)	Decreased RBCs, WBCs, lymphocytes and neutrophils
Case-Control	Rothman et al. (1996a)	Decreased lymphocyte counts, benzene metabolites
Case-Control	Rothman et al. (1996b)	Decreased lymphocyte count, chromosome damage
Cross-Sectional	Collins et al. (1997)	Decreased lymphocytes
Biomarkers of Exposure		
Case-Control	Rappaport et al. (2002)	Benzene metabolites
Case-Control	Rothman et al. (1995)	Chromosome damage
Case-Control	Rothman et al. (1998)	Benzene metabolites
Acronyms: AMML = acute myelogenous and monocytic leukemia; ANLL = acute non-lymphocytic leukemia; ALL = acute lymphocytic leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; HL = Hodgkin's lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; RBC = red blood cell; WBC = white blood cell.		

Benzene Health Effects

This section describes the various health effects that we identified in the literature review as having a potential link to benzene exposures. A number of effects have been studied, with varying levels of support in the literature. Exhibit 2 presents IEc's assessment of the strength of evidence supporting a relationship to benzene exposure for each health effect.

EXHIBIT 2 BENZENE HEALTH EFFECTS WEIGHT OF EVIDENCE	
Health Effect	*Strength of Evidence*
Leukemia (all types)	High
Acute Myelogenous	Medium
Acute Lymphocytic	Low
Chronic Myelogenous	Low
Chronic Lymphocytic	Low
Multiple Myeloma	Low
Myelodysplastic Syndrome	Low
Hodgkin's Lymphoma	Low
Non-Hodgkin's Lymphoma	Low
Decreased Lymphocytes	High

Leukemia

Significantly increased risks of leukemia have been consistently reported in benzene-exposed workers of various industries, leading EPA to classify inhaled benzene as a "known/likely" human carcinogen under the proposed 1996 cancer guidelines. In the EPA document *Carcinogenic Effects of Benzene: An Update* (EPA, 1998), it states "[e]pidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and leukemia" (page 4). Our literature review also supports a link between benzene exposure and leukemia.

There are two cohorts in particular that EPA describes, which have been extensively studied and peer-reviewed. The first consists of a group of 1,717 white male workers employed in Pliofilm manufacturing plants located in Ohio between 1940 and 1972 (hereafter, the "Pliofilm Cohort").[2] The second is a cohort of 74,828 workers in a variety of industries in China employed between 1972 and 1987 (hereafter, the "Chinese Worker Cohort") studied jointly by the US National Cancer Institute (NCI) and the Chinese Academy of Preventative Medicine (CAPM). Results from these retrospective cohort studies indicate an association between exposure to a range of benzene concentrations and an elevated risk of leukemia (all types). Recent analyses comparing exposed workers to unexposed workers in the Chinese Worker

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[2] Pliofilm is a glossy membrane made from rubber hydrochloride and used chiefly for water-resistant materials and packaging (Crump, 1994).

Cohort show significant elevated relative risks (RRs) of leukemia incidence of 2.6 (95%CI: 1.3, 5.7) (Yin et al., 1996) and 2.5 (95% CI: 1.2, 5.1) (Hayes et al., 1997). In other words, the exposed workers were roughly two and a half times more likely to develop leukemia than the unexposed workers. Similarly, a recent Pliofilm Cohort analysis found an elevated standardized mortality ratio (SMR) of 2.9 (no 95% CI provided), comparing the observed cases of leukemia in the cohort to an expected number of cases based on US sex- and age-specific rates.

Through our literature review, we identified several other recently published epidemiologic studies that have found an overall increase in risk of leukemia (all types) with exposure to benzene, or a trend of increasing relative risks with increased exposure to benzene (Ireland et al., 1997; Costantini et al., 2003; Adegoke et al., 2003; Sorahan et al., 2005; Guenel et al., 2002; Bloemen et al., 2004; Glass et al., 2003; Collins et al., 2003).

Leukemia Subtypes

There are four types of leukemia: Acute Myelogenous Leukemia (AML) (also referred to as Acute Myelogenous and Monocytic (AMML) or Acute Non-Lymphocytic Leukemia (ANLL)), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), and Chronic Lymphocytic Leukemia (CLL). The strength of evidence supporting a link between benzene and specific types of leukemia varies. AML has the most evidentiary support for a link with benzene exposures out of all of the four subtypes of leukemia, but some of this evidence is conflicting. EPA concludes "[a] number of studies, including the Pliofilm cohort, have indicated that benzene exposure is associated with various types of lymphohematopoietic neoplasia other than ANLL (Savitz and Andrews, 1996). However, the specific types associated with benzene exposure remain unidentified" (EPA, 1998, page 5).

Our research uncovered associations between benzene and AML in the literature, including both of the major cohort studies. The Chinese Worker Cohort found an elevated RR of ANLL incidence of 3.0 (95% CI: 1.0, 8.9) and 3.1 (95% CI: 1.2, 10.7) (Hayes et al., 1997; Yin et al., 1996) and the Pliofilm Cohort identified a RR of AML deaths of 5.03 (95% CI: 1.84, 10.97) (Wong, 1995). The Pliofilm Cohort analysis also found evidence for an increasing trend of AML with increasing cumulative exposure to benzene (Crump, 1994, 1996; Wong, 1995). In addition, a study by Glass et al. (2003) found a significantly increased relative risk of ANLL among petroleum workers at much lower levels of exposures. The authors found a RR of 7.17 (95% CI: 1.27, 40.4) for workers exposed to greater than 8 ppm-years of benzene compared with those exposed to less than or equal to 4 ppm-years. The wide confidence bounds associated with this estimate, however, are evidence of statistical instability, calling into question the validity of the Glass et al. results. Other recent studies that we identified through the literature search have not found the same strength of association, finding only non-significantly elevated risks of AML with benzene exposure (Rushton and Romaniuk, 1997; Ireland et al., 1997; Adegoke et al., 2003; Sorahan et al., 2005; Bloemen et al., 2004; Guenel et al., 2002; Collins et al., 2003). These studies suffer from methodological weaknesses such as small numbers of cases and possible exposure misclassification, which may have limited their ability to detect an association. (See the summary table in Attachment 1 for specific strengths and weaknesses of the individual studies).

Very few studies have shown an increase in risk due to the other leukemia subtypes aside from AML. EPA (1998) concluded that there may be evidence supporting an association of

benzene with CML and CLL. They cite a study by Rushton and Romaniuk (1997) that found a non-significant increase in risk of CLL in petroleum workers in the UK whose benzene exposure increased with duration of employment.

We attempted, through the literature search, to find evidence supporting a link between benzene and specific non-AML leukemia subtypes. We found that Hayes et al. (2000) reported non-significant elevated relative risks for CML (RR = 2.6) and ALL (RR = 2.8), but also reported small numbers of cases for these two subtypes, making the results unstable. Another recent study found significant results for CML with an odds ratio (OR) of 2.4 (95%CI: 1.3, 4.7) comparing workers that were ever exposed with those who were never exposed to benzene. In addition, the authors found a significant trend for risk of CML with increasing duration of exposure (Adegoke et al., 2003). However, this study used self-reported exposure estimates, which are likely to be affected by recall bias, so these results should be interpreted with caution.[3] Several studies found no significant results for the non-AML subtypes (Sorahan et al., 2005; Bloemen et al., 2004; Ireland et al., 1997; Glass et al., 2003; Collins et al., 2003). Because chronic leukemias are rare, and because ALL tends to occur in children more often than adults, it is possible that the occupational cohort studies available do not have large enough study populations to detect associations between benzene and these leukemia subtypes, especially if the association is weak. Furthermore, with such small numbers of cases, any errors in disease classification due to imprecise or inaccurate diagnoses could have a substantial impact on whether or not a study finds an association.

Hodgkin's and Non-Hodgkin's Lymphomas

Few studies exist that examine an association between benzene exposure and either Hodgkin's Lymphoma (HL) or Non-Hodgkin's Lymphoma (NHL).[4] The IRIS support document for benzene carcinogenicity cites results from the Chinese Worker Cohort that showed a significantly elevated relative risk of developing NHL for benzene workers with 10 or more years of benzene exposure (RR = 4.2 (95%CI: 1.1, 15.9) (Hayes et al., 1997). However, this estimate is fairly unstable, as indicated by the wide confidence bounds, and has not been confirmed through the results of other, more recent epidemiologic studies (Sorahan et al., 2005; Bloemen et al., 2004; Schnatter et al., 1996a; Glass et al., 2003; Collins et al., 2003). In addition, two meta-analyses, one of 26 cohorts of petroleum workers, which included a total of 506 deaths from NHL (Wong and Raabe, 2000), and one consisting of 21 occupational study groups and 404 cases of NHL (Lamm et al., 2005) did not find positive associations with exposure to benzene, reporting SMRs of 0.90 (95%CI: 0.82, 0.98) and 1.04 (95%CI: 0.94, 1.14) respectively. An abstract presented at the *Recent Advances in Benzene Toxicity* conference in Munich,

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[3]Recall bias occurs when cases and controls differentially recall events related to their exposure. This can occur because cases tend to scrutinize their exposure history more closely than controls (Gerstman, 1998).

[4] Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma are both cancers that start in the lymphatic tissue, often in the lymph nodes. Cancerous cells in Hodgkin's disease are called Reed-Sternberg (R-S) cells, and are different from the cells of non-Hodgkin's lymphoma. Scientists believe that the R-S cells are a type of malignant B lymphocyte (Medline Plus, a service of the US National Library of Medicine: http://medlineplus.gov/).

Germany, reviewed the relationship between benzene and NHL, and concluded that "most studies do not find an association between benzene exposure and NHL" (Lamm et al., 2004).

Of the studies that we identified that looked at the risk of HL related to benzene exposure, none of them found positive results (Sorahan et al., 2005; Bloemen et al., 2004; Ireland et al., 1997; Schnatter et al., 1996a; Collins et al., 2003; Swaen et al., 2005).

Multiple Myeloma

A few studies cited in the IRIS support document, including a case study (DeCoufle et al., 1983) and the analyses of Pliofilm Cohort (Rinsky et al., 1987; Wong, 1995) found an increased risk of multiple myeloma associated with benzene exposure. Several recent studies, however, including large-scale cohort studies, have failed to confirm this, and have found no associations or weak associations between benzene and multiple myeloma (Hayes et al., 1997; Ireland et al., 1997; Sorahan et al., 2005; Schnatter et al., 1996a; Glass et al., 2003; Swaen et al., 2005; Collins et al., 2003). In addition, two reviews examining the literature linking multiple myeloma and benzene exposure conclude that "benzene exposure is not a likely causal factor for multiple myeloma" (Bezabeh et al., 1996) and that there is "no scientific evidence to support a causal relationship between exposure to benzene … and the risk of developing multiple myeloma" (Bergsagel et al., 1999). A meta-analysis of case-control studies supports these conclusions, finding an OR of 0.74 (95%CI: 0.6, 0.9) for multiple myeloma for those with occupational exposure to benzene or organic solvents (Sonoda et al., 2001).

Myelodysplastic Syndrome

We found no evidence for an association between benzene and myleodysplastic syndrome (MDS) alone, but found a positive RR for a combined outcome of MDS/ANLL in the Chinese Worker Cohort of 4.1 (95%CI: 1.4, 11.6) (Hayes et al., 1997). The fact that MDS is a known precursor to AML makes it difficult to assess the effects of benzene on MDS separately from those on AML. In addition, Hayes et al. (2001) notes that Chinese Workers diagnosed with MDS were originally diagnosed as having ANLL. The similarity in clinical characteristics of these two conditions could lead to misclassification of the outcome, making an analysis of the effects of benzene on MDS challenging.

Additional Cancerous Endpoints

EPA discusses other cancerous endpoints in addition to leukemia in their benzene carcinogenicity update (EPA, 1998). They cite animal studies that have found cancer in multiple target organ sites such as oral and nasal cavities, liver, forestomach, preputial gland, lung, ovary, and mammary gland. We found no epidemiologic evidence to support these associations in our literature review.

In addition, EPA's carcinogenic assessment of benzene discusses the evidence for a link between parental occupational exposure to benzene and childhood leukemia. Although a handful of studies have found positive associations there is not conclusive evidence for this link (see EPA, 1998, page 42). EPA concludes "data to make quantitative adjustments for [increased risk

due to parental occupational exposures to benzene] do not exist at this time" (EPA, 1998, page 42). We did not find any additional studies on this topic in our literature search.

Non-Cancerous Effects

Benzene has been associated with a number of non-cancer health effects; however, many of these appear unlikely to occur at levels expected to be found in ambient air (less than 10 ppb, based on EPA's NATA study). Benzene exposure at high concentrations has been associated with various hematological abnormalities, including aplastic anemia.

EPA developed a reference concentration (RfC) of 0.03 mg/m^3, based on a critical effect of decreased lymphocyte count from a cross-sectional study by Rothman et al. (1996a), which analyzed 44 members of the Chinese Worker Cohort data. This study found blood cell effects at exposure concentrations of about 8 ppm. The EPA support document for non-cancerous effects (EPA, 2002) identified additional studies that have also found decreases in hematologic factors (Ward et al., 1996; Bogadi-Sare et al., 2000) but that do not provide sufficient data to assess a LOAEL or NOAEL. In addition, EPA recognized some studies that did not find positive associations between benzene and hematologic factors, making these studies unsuitable for establishing a LOAEL (Khuder et al., 1999; Collins et al., 1991).

We identified two recent case-control studies that found statistically significant decreases in lymphocyte counts in workers with low exposure concentrations of less than 1 ppm (Lan et al., 2004) and less than 0.25 ppm (Qu et al., 2002). These studies both used high quality exposure assessment (personal monitors) and controlled for important confounding factors. In addition, we found a study by Collins et al. (1997) that does not show positive results for workers with an average exposure of 0.55 ppm, but this study relied on historical exposure data and blood samples collected through a medical surveillance program, making the results somewhat uncertain.

Issues Related to the Leukemia/Benzene Dose-Response Function

Epidemiologic Evidence for the Dose-Response Function

EPA supports the use of data from the Pliofilm cohort for quantifying the dose-response relationship between inhaled benzene and leukemia. A range of unit risk values is provided on EPA's IRIS for an individual exposed over a lifetime to 1 µg/m^3 of benzene in air. The unit risk range, 2.2×10^{-6} to 7.8×10^{-6}, is based on Crump's 1994 analysis of the Pliofilm cohort, with lower and upper bounds derived using a linear dose-response model and Paustenbach (1992) and Crump and Allen (1984) exposure estimates, respectively.

EPA recommends using the Pliofilm cohort because of methodological weaknesses in the Chinese Worker Cohort, such as confounding by exposure to other chemicals, and potential exposure misclassification. EPA states in the IRIS support document for benzene that "[t]he derivation of the cohort from many different factories across China suggested the possibility that this cohort was exposed to mixtures of many different chemicals…[which] could have produced confounding effects, especially if exposures were to chemicals that increase the risk of leukemia" (EPA, 1998, page 13). The Pliofilm cohort workers, on the other hand, were exposed primarily

to benzene, with little exposure to other chemicals. EPA also found that the exposure assessment used with the Chinese Worker Cohort was flawed. EPA states that "only 38% of the exposure estimates were based upon actual measurements of benzene concentrations; the remainder were numbers generated by factory industrial hygienists based upon their estimates of benzene concentrations" (EPA, 1998, page 13). Therefore, EPA concludes that the dose per individual could have been subject to random error and to bias, which could have affected the shape of the dose-response relationship.

We found several additional cohort and case-control studies examining the relationship between benzene exposure and leukemia (Guenel et al., 2002; Costantini et al., 2003; Adegoke et al., 2003; Sorahan et al., 2005; Bloemen et al., 2004; Rushton and Romanieuk, 1997; Schnatter et al., 1996a; Swaen et al., 2005; Collins et al., 2003; Glass et al., 2003). The SAB HES, in their review of our original analytical plan, cited two of these studies (Rushton and Romanieuk (1997) and Schnatter (1996a)) as examples of studies finding an association at levels closer to those likely to be modeled in the case study. These studies involve analyses of two cohorts of petroleum workers, one in the United Kingdom and one in Canada, who are known to have low average exposures (e.g., less than 5 ppm (Rushton and Romanieuk, 1997)). In a nested case-control analysis, Rushton and Romanieuk compared 91 cases of leukemia to matched controls and found a slightly elevated relative risk for increasing cumulative exposure (1.004 (95% CI: 0.99, 1.02). However, incomplete or missing exposure information limit the usefulness of these results. Twenty percent of work histories were incomplete, and assumptions were made for missing exposure data such as hygiene data for base estimates, data on closed terminals, and product source, which contributed to uncertainties in the exposure estimates (Rushton and Romanieuk, 1997). Similar results were found for the Canadian cohort, which compared 14 cases of leukemia with matched controls and found a non-significant odds ratio of 1.002 for each ppm-year of exposure (95% CI: 0.989, 1.015). The authors of this study acknowledge that the lack of finding of a dose-response relationship between cumulative benzene exposure at low levels and leukemia may be due to limited statistical power deriving from small sample size.

The other recent cohort and case-control studies that have looked at the association between benzene and leukemia suffer from methodological weaknesses, such as small cohort size, insufficient exposure assessment, and potential confounding of other exposures that limit the usefulness of these studies for our analysis (see Attachment 1 for a summary of the limitations of each study). We will focus the remainder of this discussion on the most extensively studied and peer-reviewed cohorts; the Pliofilm Cohort and the Chinese Worker Cohort. Exhibit 3 below compares the characteristics of the two cohorts, highlighting methodological strengths and weaknesses of each.

EXHIBIT 3 **COMPARISON OF THE PLIOFILM COHORT AND THE CHINESE WORKER COHORT**		
	Pliofilm Cohort	**Chinese Worker Cohort**
Description of Industry	Workers in Pliofilm manufacturing plants in two locations in Ohio	Workers in 672 factories in 12 cities of China employed in a number of industries such as painting, printing, footwear, rubber, and chemical
Cohort Size/Number of Leukemia Cases	1,717 white males/14 cases of leukemia	74,828 benzene exposed workers/47 cases of leukemia
Dates of Employment/ Follow-up	1939-1976/Follow-up through 1987 Rinsky et al. (2002) followed subjects through 1996.	1972-1987
Exposure Levels with Positive Effects	>40 ppm (cumulative exposure)	<10 ppm (average exposure); <40 ppm-years (cumulative exposure)
Exposure Assessment Method	Crump and Allen (1984) updated the exposure assessments made in Rinsky et al. (1981) by estimating calendar-specific benzene concentrations for various work areas, allowing for the creation of a complete exposure profile for each worker. Paustenbach et al. (1992) made a detailed reevaluation of exposures in this cohort that incorporated information obtained from historical records and interviews with former workers. This newer assessment accounted for dermal exposures, short-term high-level exposures, respirator use, biases of sampling devices used in earlier years, and a previously unaccounted for shutdown of the St. Mary's plant during World War II.	Work history data for each worker was merged with exposure data based on job title, using measurement data and historical information such as product use in each factory (Dosemeci et al., 1994).
Major Results	RR comparing total observed leukemia deaths to expected deaths, based on US sex- and age-specific rates = 2.9. Found that multiplicative, linear models were the best fit for the dose-response data (Crump, 1994).	Incidence of leukemia in all exposed subjects compared to unexposed subjects, RR = 2.5 (1.2, 5.1), controlling for age and sex. Significant trend for increasing RRs with increasing exposure category (p = 0.04) (Hayes et al., 1997).
Strengths	-Workers exposed to benzene primarily (not likely to have significant exposures to other carcinogens) -Thorough exposure assessment -Dose-response relationship investigated for leukemia deaths, and betas reported per ppm-year	-Larger number of cases of leukemia -Positive results seen at lower benzene exposures
Limitations	-Relatively smaller number of cases of leukemia -Benzene exposures higher than those experienced by the general public -No measurement data available prior to 1946.	-Workers may have been exposed to a variety of other carcinogens in addition to benzene -Exposure estimates have been criticized as underestimates (only 38/% of exposure estimates were based on measurements) -No results for increased risk per ppm-year

Health Endpoints Considered: One difference between the two cohort studies is the endpoint examined. The Chinese Worker Cohort reported leukemia incidence, while the Pliofilm Cohort reported leukemia deaths. Therefore, the Pliofilm study could have underestimated cases of leukemia by only reporting deaths. However, survival rates for leukemia during the time of the Pliofilm Cohort were low, leading us to assume that leukemia deaths and leukemia incidence may be considered reasonably equivalent.

Exposure Assessment: Both the Chinese Worker Cohort and the Pliofilm Cohort analyses are retrospective cohort studies, making historical exposure assessment challenging. Dosemeci et al. (1994) state that 38 percent of the exposure estimates in the Chinese Worker Cohort are based on monitoring data. The Pliofilm Cohort data are based on monitoring data that varies in quantity with time and by site. For instance, the number of samples increases over time, with very little data on exposures before 1950. Also, the Akron I plant has virtually no measurement data, while the St. Mary's plant has a great deal.[5] The inconsistency in monitoring data for both cohorts makes the exposure assessments for both of these analyses somewhat uncertain.

Exposure assessment for the Pliofilm Cohort has been investigated by three separate research groups, Rinsky et al. (1981 & 1987), Crump and Allen (1984), and Paustenbach et al. (1992), yielding a variety of results. The different exposure assessment results of these three analyses can be attributed to various assumptions made by the investigators in relation to exposure of the workers, such as exposure concentrations experienced before sufficient monitoring data was available. Paustenbach et al. estimates are the highest, followed by Crump and Allen, and then Rinsky et al. Accordingly, the Rinsky et al. estimates yield higher relative risks than the other two exposure estimates. The estimates by Paustenbach et al. (1992) have been criticized in a paper by Utterback and Rinsky (1995). These authors contend that the Paustenbach et al. exposure estimates were based upon worst-case assumptions for the exposure scenarios that existed during the early years of the cohort. In addition, Utterback and Rinsky noted that prolonged exposure to the high levels of benzene estimated by Paustenbach et al. would have resulted in much higher prevalence of benzene poisoning than was actually seen in the cohort. EPA points out, however, that despite differences in the three sets of exposure estimates, the cumulative SMRs from the three studies differ by no more than a factor of 2.5 (see EPA, 1998, Table 2, Page 10).

The Chinese Worker Cohort has one set of exposure estimates, as described by Dosemeci et al. (1994). These exposure estimates have been criticized by Wong (1999 & 2002) and Budinsky et al. (1999). The authors state that these exposure estimates are not consistent with exposure measurements provided by the CAPM investigators before NCI's involvement or with studies providing air monitoring data. Wong and Budinsky et al. conclude that Dosemeci et al. exposure estimates are likely to be underestimated, based on these other available measurements. Budinsky et al. also points out that benzene poisoning is a biomarker for benzene exposure, and incidence of chronic benzene poisoning seen in a study based on the Chinese Worker Cohort (Yin et al., 1987) suggests higher exposures were experienced by the workers than those reported in Dosemeci et al. (1994). The review authors also cite a number of other limitations of the

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[5] See Paustenbach et al. (1992), Figure 3, page 183 for details on sampling data.

exposure assessment, such as poor exposure assumptions (relating to the percentage of benzene in various products used in the factories), inconsistencies in calculating individuals' exposures, wide exposure categories, and an inadequate validation study. Specifically, Wong (1999) states that the results of the validation study by Dosemeci et al. (1996) only indicate that exposure estimates are valid in relation to each other, and one could find a similar upward trend as described in the validation results if benzene exposure levels were underestimated.

Authors of the Chinese Worker Cohort analyses published a response to the criticisms outlined by Wong and Budinsky et al. (Hayes et al., 2001). They acknowledge that the estimates are not consistent with exposures in recently published papers using monitoring data, but argue that these measurements were only taken in a small number of workplaces that would not necessarily be reflective of concentrations found in all of the 672 factories in the Chinese Worker Cohort studies. In addition, they state that exposure measurements taken during the CAPM studies were not systematized, were taken during a time period when benzene exposures were higher, and were taken at a single point in time, making them less suitable for personal exposure assessment. They also defend their estimates against internal consistencies, saying that there were differences in reporting between two CAPM papers, but that these exposure estimates were not carried through to the NCI-CAPM studies. Finally, the authors support their validation study (Dosemeci et al., 1996) by stating that the results showed a clear dose-response relationship between benzene exposures and benzene poisoning, which provides evidence of the predictive capacity of the exposure assessment and of the accuracy in the quantitative estimation of benzene exposure.

Confounding Factors: The two main cohorts also differ in the amount of exposure that the workers had to other potential carcinogens. Wong (1999) mentions that in the original analysis by Yin et al. (1987), 95 percent of those in the Chinese Worker Cohort were exposed to chemicals other than benzene. He goes on to say that the control workers had no known exposure to benzene or other occupational carcinogens, meaning that increased risk in health effects seen in the exposed workers may reflect the effects of other occupational carcinogens in addition to benzene. The workers in the Pliofilm Cohort, on the other hand, were exposed primarily to benzene and it is likely that increased risks found in these analyses were due to benzene exclusively.

The Hayes et al. (2001) response states that the risks for ANLL/MDS were systematically increased across all of the diverse industries studied, which leads to the conclusion that the associations were due to the common exposure to benzene, rather than other carcinogens. Hayes also points out that other industrial exposures linked to benzene, such as ionizing radiation, butadiene, and ethylene oxide are unlikely to contribute to the associations seen based on occupational data from the cohort. Finally, Hayes states that elevated risk for ANLL were found in the painters who used benzene-containing paint but that painters not exposed to benzene do not show increased risks for leukemia.

Shape of the Dose-Response Function

The shape of the dose-response function for leukemia and benzene is uncertain, with different studies suggesting one or more possible functional forms (e.g., linear, supralinear). EPA acknowledges this uncertainty in the dose-response function due to questions about the

mode of action for benzene-induced leukemia. They indicate that there is conflicting information on the possibility of a threshold in the dose-response function, as well as existing data suggesting a supralinear shape at low doses. EPA concludes that the lack of effects at low levels seen in some studies may not be indicative of a threshold, but instead may be due to lack of power in current data to examine low-dose effects of benzene. They also point out that if there are individual threshold levels, due to variability in sensitivity to benzene's effects, it is unlikely that a single threshold dose could apply to an entire population exposed to benzene. Lack of consistent statistical data, coupled with evidence from studies on the mode of action of benzene (e.g., studies on benzene metabolism and chromosomal damage), and high background levels of benzene in the environment[6] lead EPA to conclude that a linear dose-response function for benzene at low doses would be sufficiently conservative, stating that "there is insufficient evidence to reject this concept [of a linear extrapolation to low doses]" (EPA, 1998, page 37).

EPA notes in the IRIS support document for benzene (EPA, 1998) the existence of some evidence for a possible threshold of benzene exposure necessary to see increased risk of leukemia. We investigated the possibility of a threshold in our literature search. Schnatter et al. (1996b) reanalyzed the Pliofilm Cohort data, calculating average total concentration per person. The authors found a "critical" concentration of 35-40 ppm when a median exposure was used (using a combination of Rinsky (1981), Crump and Allen (1984), and Paustenbach (1992) exposure estimates). In addition, Pliofilm cohort data has not found significant increases for leukemia below 40 ppm-years of exposure, which suggests a potential threshold. However, all of these findings are uncertain due to low power of these studies at low levels of exposures.

EPA pointed out in the IRIS support document for benzene (EPA, 1998), that some evidence exists for a supralinear dose-response function. For instance, Hayes et al. (1997) found relative risks for leukemia that are significantly elevated at 10 ppm of benzene, but tend to plateau as the dose increases to higher levels. However, concerns about bias in the exposure assessment for the Chinese Worker Cohort data could have contributed to a spurious supralinear dose-response reported in the studies using the historical data to calculate cumulative exposure.[7]

Studies of benzene metabolism may give some insight into the shape of the dose-response function, since animal and human studies have shown that benzene metabolites may exert the carcinogenic effects of benzene (EPA, 1998). Rothman et al. (1996b) found that formation of urinary toxic metabolites decreased from 32 percent in workers exposed to <31 ppm of benzene in air to 24 percent in workers exposed above this level, suggesting that a plateau exists for benzene effects at higher exposures. Rothman et al. (1998) found that relative levels of the benzene metabolites hydroquinone and muconic acid decreased while phenol and catechol increased in the more highly exposed workers compared with the less exposed. The authors conclude that, assuming that hydroquinone is the toxic metabolite of benzene, the results suggest that "the risk for adverse health outcomes due to exposure to benzene may have a supralinear relation with external dose" (Rothman et al., 1998, page 711). The author does point out,

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[6] High background levels of benzene could overwhelm defense mechanisms in the body that might otherwise show a threshold effect.

[7] The exposure estimates in the Chinese worker study are thought to be underestimated, which could lead to inflated relative risks at lower levels, producing a supralinear curve.

however, that urinary metabolites may not necessarily reflect metabolite concentrations in target tissues. Rothman et al. (1997) also investigated the hypothesis that individuals with mutations in genes affecting enzymes involved in benzene metabolism would be more susceptible to benzene poisoning. The authors' results supported this hypothesis, suggesting that there may be an enzyme-mediated process involved in benzene toxicity that could involve saturation of the enzyme at higher doses. This type of process would also support a supralinear dose-response curve. These studies, however, indicate that saturation in benzene concentrations likely occurs at levels much higher than those expected to be found in our case study.

We identified a study by Rappaport et al. (2002) investigating the presence of albumen adducts of benzene oxide (BO-Alb) and 1,4-benzoquionone (1,4-BQ-Alb) in the blood of workers exposed to low levels of benzene in China. Exposure in this study was measured with personal benzene monitors. The authors found a supralinear dose-response for benzene exposures and production of Bo-Alb and 1,4-BQ-Alb with deviations from linearity beginning at 1 ppm. The authors attributed this to saturable metabolism of benzene at that concentration.

We found further evidence for a supralinear dose-response function from another study by Rothman et al. (1995), which found an association between cumulative exposure to benzene and chromosome damage, which is thought to be a factor in the development of leukemia. The authors found a trend of increasing variants at a gene locus that suggests gene-duplicating mutations with increasing cumulative exposure to benzene. They reported a significant supralinear trend for this relationship ($p = 0.0002$). The results of this study may show a spurious supralinear dose-response relationship with benzene because of potential exposure misclassification, since its exposure estimates were based on Dosemeci et al. (1994).

Linear models were found to be the best fit in the Crump (1994) analysis of the Pliofilm Cohort. The author concluded that "[t]here was no indication of either [cumulative exposure]-dependent or intensity-dependent nonlinearity in the dose responses for any model based on the Crump and Allen exposure matrix" (Crump, 1994, page 234). Only borderline significant results were found for a intensity-dependent nonlinear model, using the Paustenbach exposure estimates.

EPA (1998) concludes that "[t]oo many questions remain about the mode of action for benzene-induced leukemia for the shape of the dose-response function to be known with certainty" (page 34). According to EPA's *Guidelines for Carcinogen Risk Assessment*, linear extrapolation to low doses should be used when there is insufficient data to establish a mode of action (MOA) as a default approach because linear extrapolation "generally is considered to be a health-protective approach" (EPA, 2005, page 3-21).

Cessation Lag

The term "cessation lag" refers to the estimate of how quickly cancer risks in a population will decline to a new steady-state level following a reduction in exposure. In their review of the analytical plan for the benzene case study, the SAB HES subcommittee suggested that we revisit our proposed five-year "cessation lag" for benzene-induced leukemias in light of evidence from available epidemiologic studies. Exhibit 4 summarizes the findings of the studies

in our literature review with respect to the issue of latency or cessation lag of benzene-induced leukemias.

Only one study in Exhibit 4, Silver et al. (2002), explicitly modeled the cessation lag concept, using an analysis stratified on time since last exposure. All the other studies included in their models some estimate of latency, i.e., the delay between the critical exposure and diagnosis of disease or death. While not the same as the cessation lag, information about latency can also help inform our estimate for a cessation lag.

EXHIBIT 4 SUMMARY OF FINDINGS – LATENCY / CESSATION LAG ASSOCIATED WITH BENZENE-INDUCED LEUKEMIA		
Study	**Lags Tested**	**Findings**
Silver et al. (2002)	Time since last exposed: 0; 0.01-4.9; 5-19.9; and >20 years	Generated SMRs for yearly follow-ups of Pliofilm Cohort starting in 1940 and extending from 1950 through 1996. Used Cox models to estimate effect of follow-up time on risk estimates. Stratified analysis of time since last exposed to benzene suggests that for this cohort, relative risk peaks in the first few years after cessation of exposure and that exposures 5-10 years prior to the cutoff have the most impact on risk. The results suggest that ensuring maximum protection for benzene workers requires assessing risk at its peak of 5-10 years since exposure.
Finkelstein (2000)	Exposure windows: 1-4, 5-9, 10-14, 15-19, 20-24, and 25-29 years before death	Case-control study in which the exposures of subjects with leukemia and matched controls were compared at various times before the death of the case. Looked backward from the date of death of the case subjects and compared the exposures of case and control subjects in specific exposure windows prior to the death of cases. Found no significant difference in the benzene exposures of subjects with leukemia and their matched controls 15 or more years prior to death of case. The highest risk was related to exposures incurred in the previous 10 years.
Hayes et al. (1997)	Recent (1.5-10 years) Distant (10+years)	Study of Chinese Worker Cohort that partitioned cumulative exposure into recent (1.5-10 years earlier) and distant (10 or more years earlier) exposure. Risk of ANLL/MDS was positively associated with recent benzene exposure, and additional distant exposure did not appear to further increase risk.
Crump (1994)	0, 3, 5 years	For the best-fitting class of risk models (multiplicative risk models using cumulative exposure), 5-year lag provided best fit to the data. Multiplicative risk models using weighted exposure generated estimates of latency for leukemia deaths of 6.7 yrs (AMML) and 7.7 years (all leukemia).
Rinsky et al. (2002)	0, 2.5, 5, and 10 years	Follow-up analysis of the Pliofilm Cohort (extended follow-up an additional 15 years). Study included at least 20 years of follow-up for every member. Model fit worsened with increasing lag. Zero lag linear model showed best fit, though 2.5 year lag only slightly less suitable. No data shown for longer lags.
Glass et al., 2004	≤15, >15 years	Nested case-control study of Australian petroleum workers (Health Watch cohort). Found that leukemia was most strongly associated with benzene exposures within 15 years of diagnosis; exposures more than 15 years prior to diagnosis showed little impact on risk.
Rushton and Romaniuk (1997)	0, 5, 10 years	Case-control study of petroleum workers in the UK. For all leukemia, risks did not change substantially with increasing lag. For AML, odds ratios for categories of cumulative exposure tended to increase with

		increasing lag, model fit tended to improve.
Schnatter et al. (1996a)	0, 5 years	Case-control study of petroleum workers in the Canada. Effect of lag on risk estimates was inconsistent.
Guenel et al. (2002)	2, 5, 10 years	Case-control study of utility workers in France. Results largely similar for different lags.
Bloemen et al. (2005)	0, 15 years	Cohort study of chemical workers assessing leukemia mortality rate. Lagging exposure by 15 years did not increase risk estimates.

Estimates of latency vary across studies. In general, most studies in Exhibit 4 found that latency estimates of 10 years or fewer fit the data best. Studies of the Pliofilm Cohort (Crump, 1994, Rinsky et al., 2002) tended to find slightly lower latency estimates, while Hayes et al. (1997) study of the Chinese Worker Cohort found stronger effects of "recent" exposures, where recent was defined as between 1.5 and 10 years prior to diagnosis. Finkelstein (2000) used the Pliofilm cohort dataset to compare exposures of leukemia cases and controls in specific exposure windows prior to the death of the case. He also found that the highest risk was related to exposures within the last 10 years prior to death, and that there was no significant difference in exposures between cases and controls 15 or more years prior to death. The case-control analysis by Glass et al. (2004) also found that exposures more than 15 years prior to diagnosis had little impact on leukemia risk. No other study found evidence suggesting a latency period longer than 15 years.

Silver et al. (2002) re-analyzed the Rinsky et al. (2002) Pliofilm Cohort dataset, generating SMRs for yearly follow-ups from 1950 through 1996. Silver et al. then analyzed these data stratified on time since last exposure and found that leukemia risk peaks within the first five years following cessation of exposure. He also found, in a separate analysis of exposure windows, that exposures five to ten years prior to the cutoff have the maximum impact on risk, and that exposures between ten and 15 years prior to cutoff may also contribute to a lesser degree. However, the authors of this study note that the smaller number of cases from the Pliofilm Cohort limits the precision with which they can define the relative risks in each period.

IMPLICATIONS FOR ANALYTICAL PLAN

This section discusses the implications of the findings of our literature review for the analytical plan for the benzene case study. We divide our conclusions and recommendations into those affecting cancer endpoints and those affecting non-cancer endpoints.

Cancer Endpoints

Based on the results of our literature review on the health effects of benzene exposure, and evidence gathered by EPA in the IRIS support document for benzene carcinogenicity, we propose to quantify the avoided cases of leukemia due to changes in benzene exposure through a dose-response analysis. We prefer to use the outcome of total leukemia for the primary estimate, since this endpoint is the most data rich, compared to the limited evidence for a link with benzene and the specific leukemia types (AML, ALL, CML and CLL). However, EPA may wish to consider conducting a sensitivity analysis that estimates avoided cases of AML, since this subtype has most evidentiary support among the different types of leukemia.

The two strongest cohort studies examining the link between benzene and leukemia have different strengths and limitations. However, the IRIS profile for benzene currently supports the use of data from the Pliofilm cohort for calculating potency estimates. Therefore, we propose to use beta coefficients reported by Crump (1994) for our primary estimate of avoided leukemias, as indicated in our analytical plan. We propose to use risk estimates based on the cumulative exposure linear multiplicative risk model presented in Crump (1994). We are not proposing to incorporate a threshold, because we do not find current evidence on potential thresholds for benzene-induced leukemia to be persuasive. In addition, although there is growing evidence supporting a supralinear dose-response function, there does not appear to be enough conclusive evidence to depart from the default linear low-dose extrapolation as discussed in EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005).

Despite its limitations, the Chinese Worker Cohort data has certain advantages over the Pliofilm Cohort, such as large sample size and benzene exposure levels that are more consistent with ambient exposures. Therefore, we could perform a sensitivity analysis using the results of the Chinese Worker Cohort. The California Environmental Protection Agency (CalEPA) recently used the Chinese Worker Cohort data in calculating a Public Health Goal for benzene (CalEPA, 2001). The CalEPA analysis of dose-response in the Chinese Worker Study could serve as the basis for our sensitivity analysis. In their analysis, the authors assumed a linear dose-response function for extrapolation to low doses. We agree with this conclusion because EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005) state that linear extrapolation should be used when the mode of action is uncertain, which is the case for benzene. In addition, given the low concentrations that are likely to be experienced in our case study, a linear approximation may be a reasonable fit, even if the overall dose-response function in supralinear, provided the data from which the extrapolation is being made are not in the plateau region of the curve.[8] Due to the growing body of evidence for supralinearity, even potentially at low doses (Rappaport et al., 2002), we could consult with the Office of Research and Development (ORD) on the usefulness of and level of effort needed to develop an alternate supralinear model for the Chinese Worker Cohort data as part of the sensitivity analysis.

In our previous analytical plan, we proposed assuming a 5-year lag between benzene exposure and leukemia as a first estimate of the cessation lag that determines the temporal distribution of benefits. Our literature search has discovered evidence that longer lag periods might also be valid, though the majority of the literature suggests that most cases would occur within 10 years, with some smaller number of cases occurring between 10 and 15 years. The Silver et al. (2002) study in particular specifically addresses the cessation lag concept and finds results suggesting that while mean latency may be in the five to ten year range, the move towards a new steady state of risk may begin fairly quickly, and a significant portion of deaths due to past exposures may occur within the first five years following a change in exposure. This finding, combined with the lag results from other studies points towards a lag structure where a new steady-state risk level is reached within 15 years following a regulatory change. Within this 15-year period, most of the risk reduction will be realized between five and ten years post-change, with smaller risk reductions accruing within the first five years and within 10 to 15 years

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[8] In this case, the linear slope might be too shallow, underestimating the true dose-response relationship at low doses. To address this, the CalEPA analysis excluded data points expected to be in the plateau region of the curve.

following the change. Identifying reasonable assumptions for distributing the risk reductions across and within these periods will require additional study of the Silver et al. paper and consultation with its authors. *[Placeholder: Refinement of the cessation lag structure may also have implications for our selection of a risk model to use in the health benefits analysis. Ideally, we would choose a model with an exposure window and lag most consistent with the proposed cessation lag. We will update this section to address this issue as the cessation lag structure evolves.]*

In addition to leukemia, benzene exposure has been associated with other cancerous health endpoints in epidemiologic studies, such as HL and NHL (Hayes et al., 1997), multiple myeloma (Rinsky et al., 1987 & 2002; Wong et al., 1995), and MDS (Hayes et al., 1997) but data on these endpoints are inconsistent and do not yet support a quantitative evaluation. We propose to describe the evidence for associations of benzene with these endpoints qualitatively.

Non-Cancer Endpoints

The dose-response data underlying the RfC (Rothman, 1996a) do not support a fully quantitative estimate of avoided "cases" of reduced lymphocytes expected at environmental levels due to the small number of data points (two). However, recent studies by Lan et al. (2004) and Qu et al. (2002), may support this effort, since they provide three and four data points, respectively, from which it may be possible to extrapolate a dose-response relationship. Other strengths of these studies include large number of exposed cases (250 and 130), detailed exposure assessment (measured), control for confounding factors, and exposure measurements below 1 ppm, which would allow for better low-dose extrapolation. Thus, quantification of "cases" may be possible, though we recommend consulting with ORD to discuss the level of effort required to pursue this approach.

Another factor to consider in deciding whether to quantify cases is the uncertain health impact of reduced lymphocytes, which would likely make it difficult to monetize such effects. The IRIS profile states that decreased lymphocyte count is a biomarker of exposure and is also thought to have a potential role as a "sentinel" effect (i.e., an early sign of toxicity in the bone marrow), but the effect itself is of uncertain clinical significance to the average population. The significance of the effect depends on both the magnitude of the decrease in lymphocytes and an individual's baseline lymphocyte level. For example, the effect of reduced lymphocytes might be more significant for individuals whose immune systems were compromised (e.g., those suffering from HIV/AIDS). Because of uncertainty in the impact on average healthy individuals, we expect we may be unable to value these avoided "cases" of reduced lymphocytes.

An alternative approach, outlined in our original analytical plan, could be to assess this endpoint by reporting the difference in the number of individuals experiencing benzene concentrations above the RfC under the pre-CAAA and post-CAAA scenarios. While we recognize that exposure above the RfC does not necessarily imply the presence of an adverse effect in a given individual, this estimate nonetheless provides some measure of progress towards reducing the likelihood of adverse hematological effects.

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